

Mechanisms of Multistage Carcinogenesis: Relevance to Bioactive Food Components

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Cancer: Multiple Causative Factors

Endogenous

Acquired

Age
Prior Exposures

ROS

Genetic

Gender
Polymorphisms

Environmental

Cig. Smoke

Env./Occup.
Chemicals

Radiation

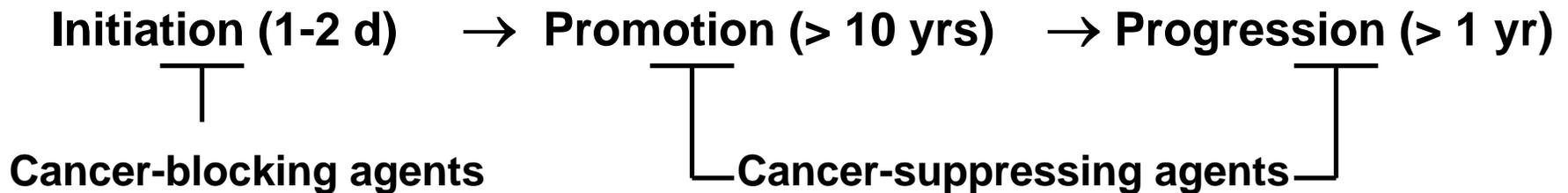
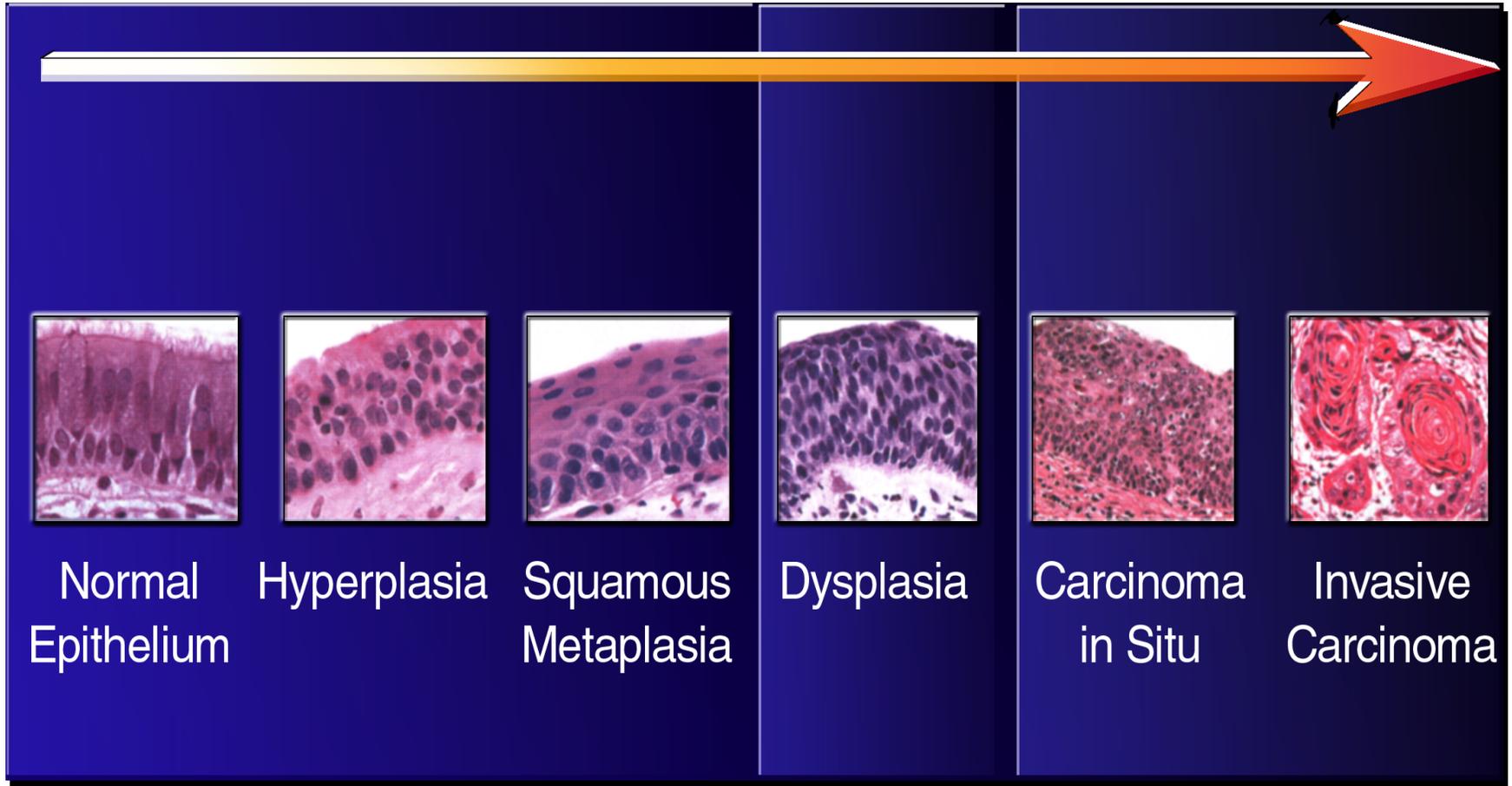
Physical agents

Dietary factors

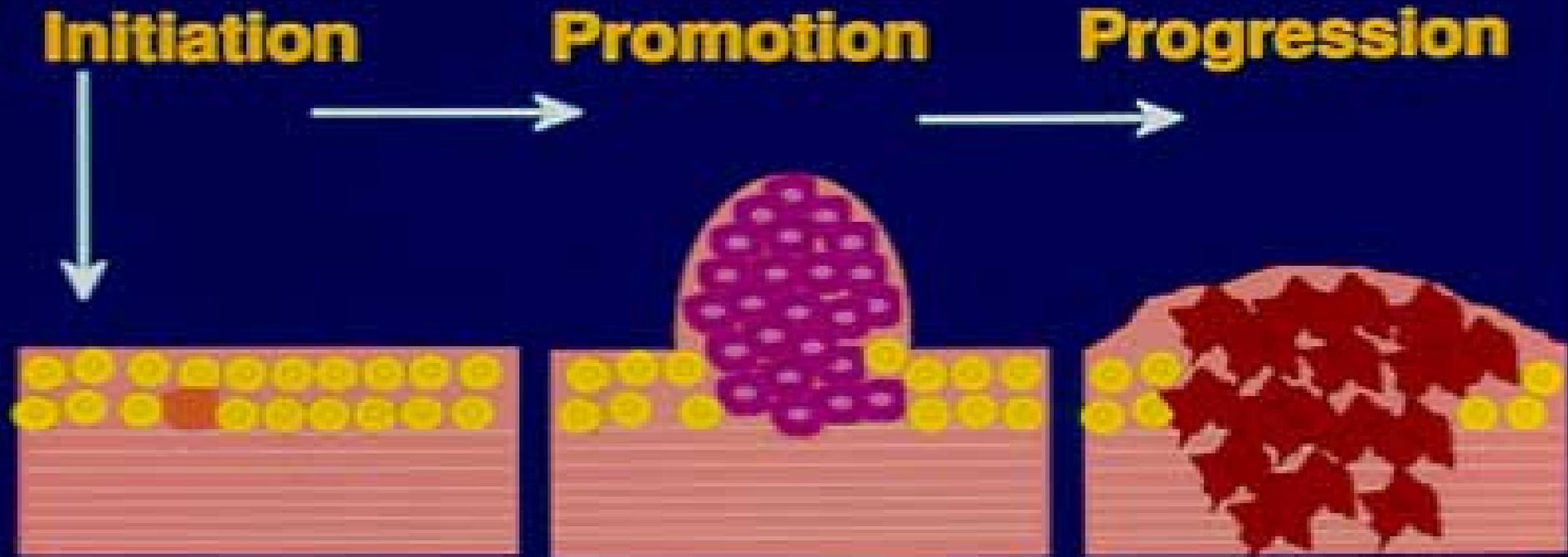
Lifestyle

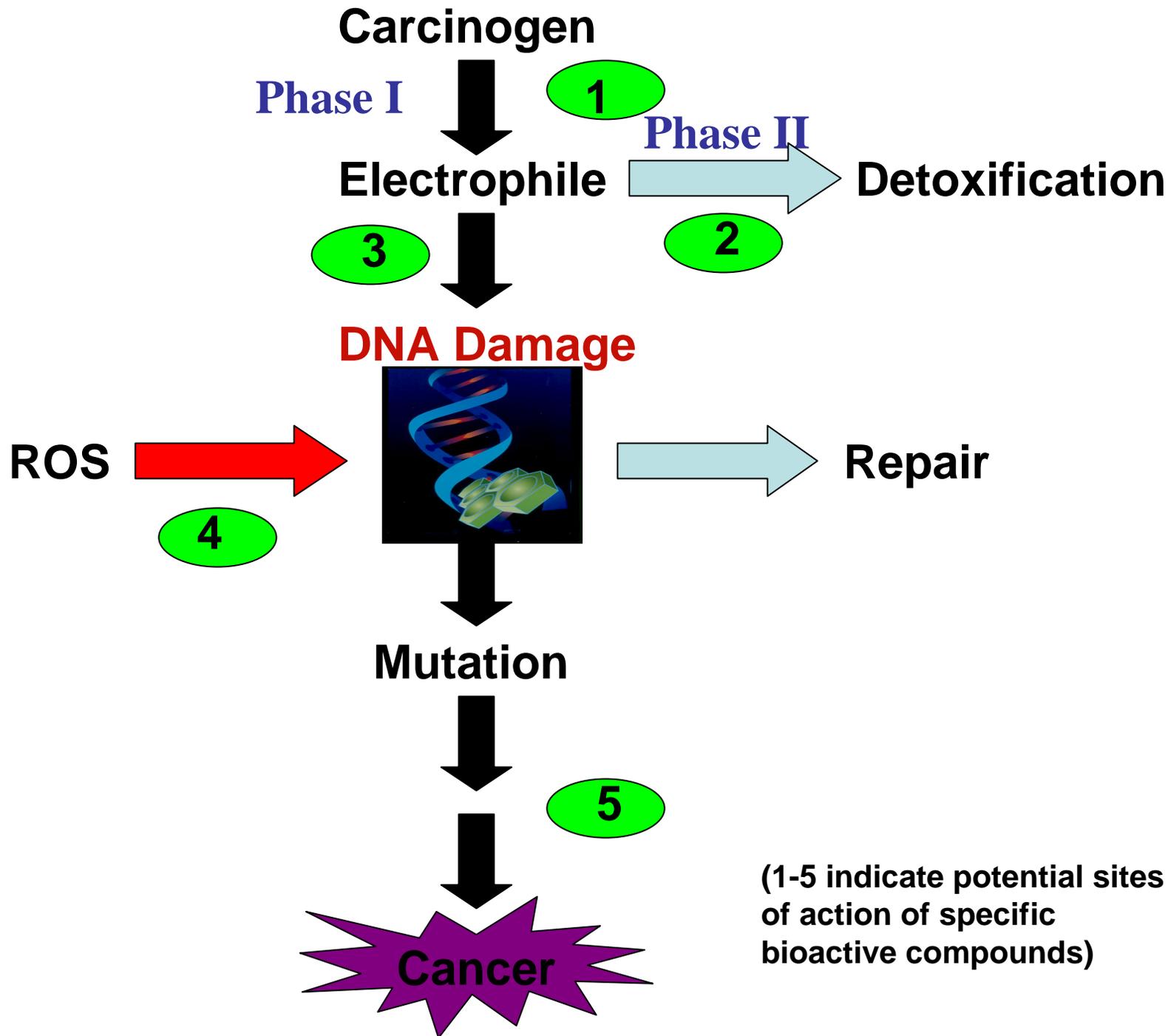
Microbes

Chemoprevention: Use of agents to inhibit, reverse or retard tumorigenesis



Genetic and Epigenetic Mechanisms





Categories of genes targeted during multistage carcinogenesis

Intracellular Circuitry

- **Agonist-induced signal transduction**
- **DNA replication and repair**
- **Cell cycle control**
- **Cell fate: survival, differentiation, senescence, and apoptosis**

Cell surface and extracellular functions

Adhesion molecule; proteases; angiogenic factors, etc

Protective Components in Diet

- 1. Fruit and Vegetables: Phytochemicals**
- 2. Fiber – colorectal cancer**
- 3. Micronutrients: Vit A, C, E, retinoids, folate**
- 4. Minerals: Calcium – colorectal cancer
Selenium – Prostate cancer**

Bioactive Food Components that Cause Cancer

<u>Compound</u>	<u>Source</u>
Aflatoxin	Mold/grains
Heterocyclic amines	Grilled meat
PAHs	"
Acrylamide	Fried foods
Pesticides	Fruits, vegetables
Arsenic	Water

Except for pesticides all of these compounds are genotoxic

Bioactive Food Components that have Anticancer Activity in Experimental Systems*

<u>Category</u>	<u>Example</u>	<u>Source</u>
Polyphenolic Compounds	EGCG Curcumin Resveritrol	green tea tumeric grapes, peanuts
Isoflavones	Genistein	Soy
Isothiocyanates	PEITC	Crucif. Veg.
Indoles	Indole-3-carbinol	Brassica veg.
Organosulfur cmpds	SAMC	garlic
Carotenoids	Lycopene	tomatoes
Vitamins**	A, C, E, D, FA	various foods
Minerals**	Se, <u>calcium</u>	

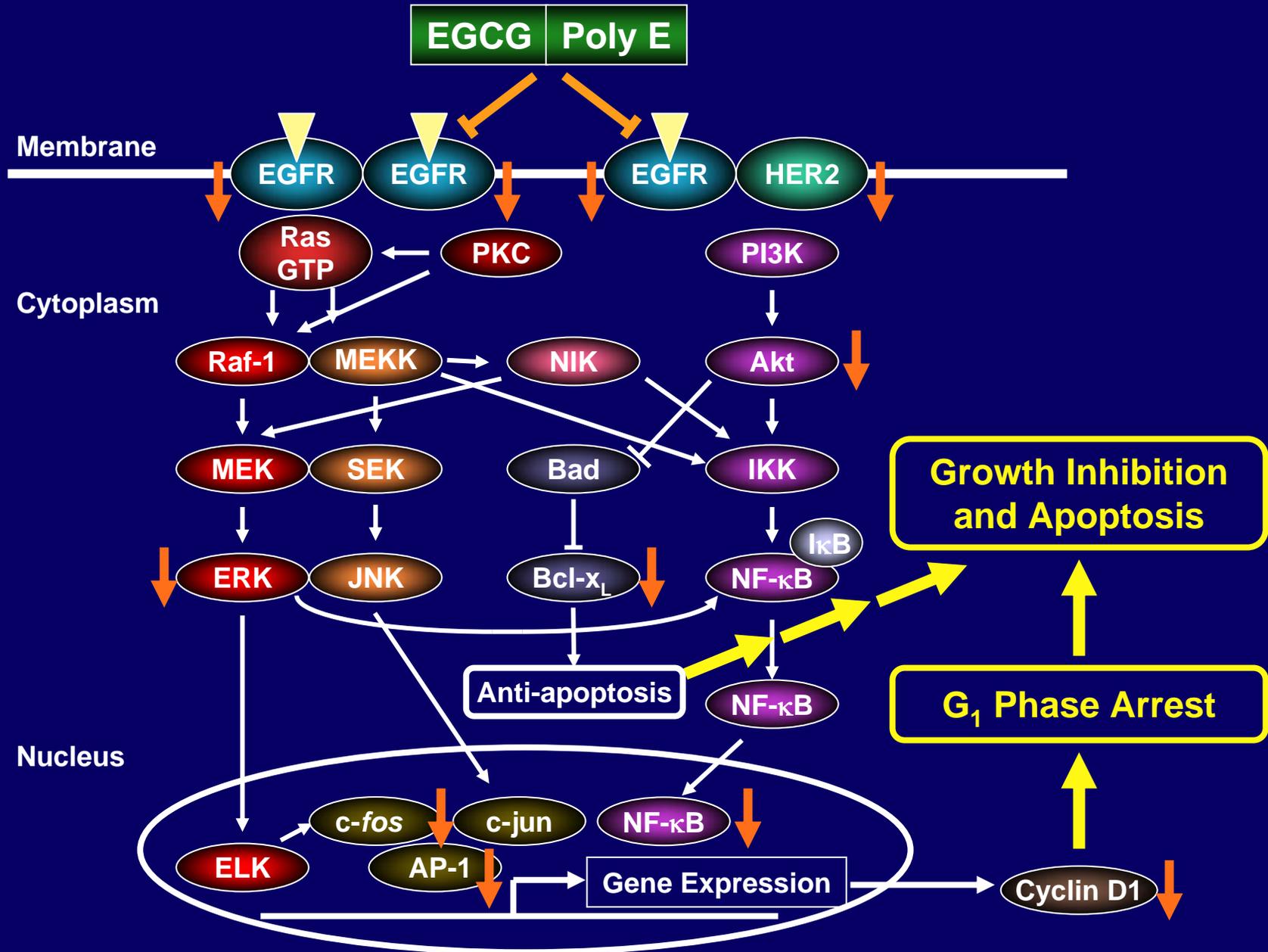
* Although epidemiologic data are suggestive for some of these compounds, none have been established as anticancer agents in humans

** Also nutrients

Cellular and Molecular Effects of Bioactive Phytochemicals

- 1. Antioxidant activity**
- 2. Modulate xenobiotic metabolizing enzymes-
carcinogen activation/detoxification**
- 3. Affect signaling molecules and gene expression:
cell cycle, cell prolif., differentiation, hormone
activity, apoptosis, angiogenesis, inflammation**

Molecular Targets of EGCG and Poly E



Future Directions/Methods

Preclinical Studies

Cell culture assays for anticancer effects

Efficacy, potency

Mechanisms of action

Reveal biomarkers

**Rodent models – including genetically engineered mice,
and biomarkers**

Randomized Clinical Trials

High risk populations

Precursor lesions

Pharmacokinetics

Biomarker

Biomarkers

Markers of oxidative damage: 8-OHdG, F₂-isoprostane

DNA adducts: BP-DNA

Serum markers: IGF1, IGFBP-3

Changes in signal transduction and gene expression in target tissues – EGFR-P, ERK-P, Akt-P, COX-2, PGE₂

**Examples: lycopene decreases serum IGF1 (Voskuil, et al., 2005);
Vit C plus E decreases BP-DNA in cig. smokers
(Mooney et al., 2005).**

Interactions Between Bioactive Foods and Hereditary Factors – Nutrigenomics

Polymorphisms/SNPs in antioxidant, DNA repair, drug metabolism, and folate metabolism genes.

Examples: High blood levels of antioxidants reduce prostate cancer risk 10-fold in men with specific SNP in MnSoD gene (Li, et al., Cancer Res., 2498, 2005). A specific SNP in XRCC1 in association with high intake fruits and vegs. may decrease breast cancer risk (Shen, et al., CEBP 14, 336, 2005).

Bioactive Compounds – General Issues

Effects of dose

Metabolism

Potential toxicity

**Interactions with other bioactive compounds,
nutrients, drugs, cigs, other environ. agents**

Special populations vs. general public

Effects on other diseases

Bioactive Compounds – Common Themes in Cancer and Cardiovascular Disease

- **Multistep process and long latent period**
- **Multifactor Causation**
- **Gene/Environment Interactions**
- **Cigarette smoke**
- **Role of inflammation**
- **Role of ROS**
- **Shared pathways of signal transduction
and gene expression**
- **Certain bioactive compounds may prevent both
diseases, i.e., polyphenolic compounds**